Original Article

Histopathological Study of Vascular Changes of Placenta in Preeclampsia Using Histochemistry

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Abstract

Context: Preeclampsia is a threat that affects globally, and more so in developing countries. It occurs in 5%–8% of pregnancies worldwide and is the second-most common cause of maternal and fetal death. **Aims:** To compare vascular changes in vessels of placental stem villi and terminal villi in the placenta in preeclampsia and compare that with placenta from normal pregnancy using special stain such as Masson's trichrome and Verhoeff's stain. **Settings and Design:** A total of 120 placentas were included in the study. Sixty cases were from preeclampsia patients of which 20 were from severe preeclampsia and 40 from mild preeclampsia and 60 were gestational age matched controls. **Subjects and Methods:** Placental tissue was examined for gross and microscopic changes. Representative sections were also screened after staining with special stains such as Masson's trichrome and Verhoeff's stain. **Statistical Analysis Used:** SPSS 22, USA, was used for descriptive and analytical data. Chi-square was the test of significance. $P < 0.05$ was considered significant. **Results:** Placenta from preeclampsia showed significantly low placental weight, less diameter, and thickness as compared to control. The stem villi showed thrombosis and medial hypertrophy. All the parameters were statistically significant when compared between the two groups, and these changes were related to the severity of preeclampsia. **Conclusions:** Vascular changes and products released may be the reason for the pathogenesis, clinical sequelae onset of disseminated intravascular coagulation, maternal inflammatory syndrome, and poor outcome in preeclampsia, which needed further study.

Keywords: Histochemistry, placenta, preeclampsia, vascular changes

Introduction

Preeclampsia is a threat that affects globally and more so in developing countries. It occurs in 5%–8% of pregnancies worldwide, and is the second-most common cause of maternal and fetal death.[1] The pathological changes in the placenta of preeclampsia reflect the pathogenesis of the disease condition. Numerous theories have been put forward to describe the pathogenesis of preeclampsia. Some of them are impaired remodeling of the spiral arteries, which becomes tortuous, thick walled, and narrow, leading to reduced blood flow. Few other theories include genetic predisposition, immunological mediated theory, the role of vasoactive agents and inflammatory changes, and oxidative stress.[2]

On microscopy, the placenta in preeclampsia shows numerous changes such as increased number of villi, prominence of villous trophoblastic cells, irregular thickening of the trophoblastic basement membrane, abundance of syncytial knot, lack of vasculo-syncytial membranes, and increased content of stromal collagen.[3] Studies done using special stains like Periodic acid–Schiff and Van Gieson in preeclampsia have shown better appreciation of histopathological changes such as increased syncytial knots, paucity of vascular syncytio membrane, basement membrane thickening fibrinoid necrosis, and stromal fibrosis of villi.[4]

The aim of this study was to compare vascular changes in stem villi and terminal villi in the placenta of preeclampsia and placenta from normal pregnancy using special stains such as Masson's trichome and Verhoeff's stain.

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Subjects and Methods

A total of 120 placenta was obtained from the Department of Obstetrics and Gynaecology of R. L. Jalappa Hospital and Research Centre to the Department of Pathology of our college. Ethical clearance was obtained from the institution.

Women with fetal congenital abnormality in newborn, twin pregnancy, hypothyroid patient and clinically detected other medical conditions such as heart disease, systemic lupus erythematous, and Rh incompatibility were excluded from the study.

The clinical history such as age of mother, blood pressure, severity of preeclampsia classified as per American College of Obstetrics and Gynecologists guidelines, and birth weight of neonate was recorded. Only the placenta from term pregnancy was collected. Gross features of placenta such as weight, diameter and thickness, nature of membrane, insertion of umbilical cord and number of vessels in umbilical cord, calcification, and infarction.

After 24 h fixation, tissue bits were taken, processed, and stained with hematoxylin and eosin and screened under the microscope for the presence of the following histopathological changes. Stem villi were looked for any medial hypertrophy and thrombosis.

Morphometry analysis for measuring villi size and medial hypertrophy was performed using Primo star Zeiss microscope, Axion cam ERc 5s Zeiss Camera, Using software ZEN2.3, version 2.3.69.01000.

Areas of fibrinoid necrosis were excluded as the morphology of villi was hampered.

The medial hypertrophy was measured in micrometer in Masson's trichrome stained slides using morphometry.

Table 1: Incidence of thrombosis and medial hypertrophy in stem villi

Parameters	Control	PE, *n* (%)	PE	
			Mild PE	Severe PE, *n* (%)
Stem villi - thrombosis	0	4 (6.67)	0	4 (20)
Stem villi - media hypertrophy	0	20 (33.33)	0	20 (100)
Total	60	60	40	20

PE: Preeclampsia

Terminal villi were looked for avascularity which was classified as large foci, intermediate foci, and small foci of avascular villi. Small foci are the finding of 3 or more foci of 2–4 terminal villi showing bland hyaline fibrosis of the villous stroma and total loss of villous capillaries. Intermediate foci are 5–10 villi, and large foci are more than 10 villi showing hyaline fibrosis. Furthermore, Verhoeff's staining was done to look for elastic content.

Statistical analysis

The data were entered into Microsoft Excel datasheet. Analysis was performed using SPSS 22 (Statistical Package for the Social Sciences version 22), USA. Chi-square test was the test of significance used to find the association between the various gross and histological parameters in the placenta from preeclampsia and that of the control group. $P < 0.05$ was considered statistically significant, while $P < 0.001$ was considered highly significant. The parameters where the Chi-square test was not applicable, Fisher exact test was used. For the sake of comparison of our studies with other studies, P value was calculated separately for mild preeclampsia and severe preeclampsia groups.

Results

The mean age of the mothers was 24.08 ± 3.90 years in the control group and 24.17 ± 3.6 in preeclampsia.

The mean birth weight was 2925.5 ± 0.49 g in control and 2251.7 ± 0.69 in preeclampsia. The result was statistically significant between the two groups ($P < 0.001$). The mean

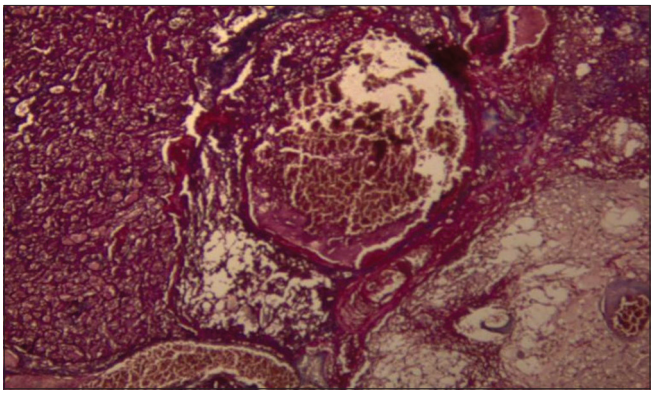

Figure 1: Thrombosis in stem villi vessel in preeclampsia.(Masson's Trichrome, ×40)

Table 2: Incidence of avascular villi

Avascular villi	Control (*n*=60), *n* (%)	PE (*n*=60), *n* (%)	PE		*P*
			Mild PE (*n*=40), *n* (%)	Severe PE (*n*=20), *n* (%)	
Small foci	6 (10)	18 (30)	18 (45)	0	<0.001
Intermediate foci	0	24 (40)	22 (55)	2 (10)	
Large foci	0	18 (30)	0	18 (90)	
Absent	54 (90)	0	0	0	

PE: Preeclampsia

placenta weight was 578.50 ± 95.36 g in control and 466.0 ± 47.34 in preeclampsia. The result was statistically significant between the two groups ($P < 0.001$).

The mean diameter of placentae in control was 20.15 ± 2.36 cm and 16.37 ± 3.81 and in preeclampsia. The result was statistically significant between the two groups ($P < 0.001$). The mean thickness of placentae of the control group was 2.73 ± 0.34 cm and 2.26 ± 0.38 cm in preeclampsia. The result was statistically significant between the two groups ($P < 0.001$).

Thrombosis of stem villi [Figure 1] was seen in 4/20 (20%) in preeclampsia while none in the control group. All four cases belonged to severe preeclampsia. Table 1: Incidence of thrombosis and medial hypertrophy in Stem villi.

The mean diameter of medial thickness [Figures 2 and 3] was 19.88 ± 1.48 um in preeclampsia and 6.43 ± 0.63 um in control. In severe preeclampsia, the mean diameter of media was 21.27 ± 1.51 and 19.18 ± 0.85 in mild preeclampsia. There were three-fold times increase in medial thickness in preeclampsia as compared to control.

Avascular villi in the control group having large foci were present in 18/60 (30%) placenta in preeclampsia, while it was absent in the control group. All the cases having large foci of avascular villi belonged to severe preeclampsia. Table 2 shows incidence of avascular villi.

Increased elastic content in terminal villi [Figures 4 and 5] was seen in 17/60 (28.33%) cases of preeclampsia. All these cases were of severe preeclampsia group while none of the placenta in mild preeclampsia and control group showed increased elastic content. Table 3 show incidence of elastic content in terminal villi.

Discussion

The placenta is a complex organ that connects the mother and fetus. Placental function is highly influenced by its anatomical structure. Morphology and cellular architecture of the placenta is important for adequate oxygen delivery to the fetus from the mother. Successful placental development is therefore essential for fetal growth and well-being after 20 weeks of gestation and is required for adequate maternal blood supply to the placenta. This has been being demonstrated by normal uterine artery Doppler.[5]

The placenta is connected to both fetus and mother. Thus, any disease process affecting the mother or the fetus also has a great impact on the placenta. Placental architecture is modified in diseases like preeclampsia affecting the mother as a result, it affects the fetus too.

Hence, this study was taken up to look into the vascular changes that occur at the level of terminal villi and stem villi as these changes have profound effect both on the fetus as well as the mother. The gross and microscopic lesions were analyzed, quantified, and compared between the two groups.

The placenta in preeclampsia showed low placental weight, less diameter, and less thickness as compared to controls and was related to the severity of preeclampsia. Table 4 shows the comparison of mean birth weight and mean placental weight.

The cause of this reduced diameter in preeclampsia was thought to be due to pathological process interfering with the normal placental growth.[6] The comparison of mean placental diameter and mean placental thickness of present study with other studies are shown in Table 5.

Thrombosis of the stem villi was seen in 4/20 (20%) cases of severe preeclampsia in the present study, while none of the mild preeclampsia and control group showed this finding. Our study was comparable with the studies done by Narasimha *et al*.[7] and Sankar *et al*.[6] Thrombosis of stem villi leads to reduces lumen of blood vessels of stem villi which in turn fails to establish a network into the terminal villi resulting in avascular villi due to the absence of capillaries. This causes reduced perfusion of the placenta, causing oxidative stress, a known mechanism in the pathophysiology of preeclampsia.

This study also showed an increase in medial thickness of the stem villi vessels in the severe preeclampsia group as compared

Table 3: Incidence of elastic content in terminal villi

Elastic content - terminal villi	Control ($n=60$)	PE ($n=60$), n (%)	PE	
			Mild PE ($n=40$)	Severe PE ($n=20$), n (%)
Present	0	17 (28.33)	0	17 (85)

PE: Preeclampsia

Table 4: Comparison of mean birth weight and mean placental weight

	Mean birth weight (g)		Mean placenta weight (g)	
	Control	PE	Control	PE
Present study	2925.5	2251.7	578.5	466.00
Salam *et al*.[3]	3460	2920	578.4	477.4
Udainia and Jain[9]	2640	2280	495	405.67
Majumdar *et al*.[10]	2800	2040	485.85	399.10
Sankar *et al*.[6]	2635.71	2037.39	470.64	401.23

PE: Preeclampsia

Table 5: Comparison of mean placental diameter and thickness with other studies

	Mean placental diameter (cm)		Mean placental thickness (cm)	
	Control	PE	Control	PE
Present study	20.15	16.37	2.73	2.26
Sankar *et al*.[6]	17.21	15.91	1.82	1.48
Kishwara *et al*.[11]	18.80	16.08	1.59	1.51
Ranga *et al*.[12]	19.1	14.1	2.4	1.9

PE: Preeclampsia

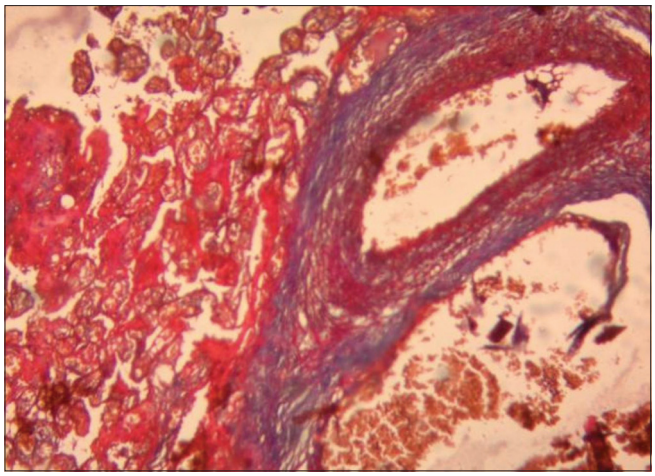

Figure 2: Medial hypertrophy in stem villi artery in preeclampsia. (Masson's Trichrome, ×4)

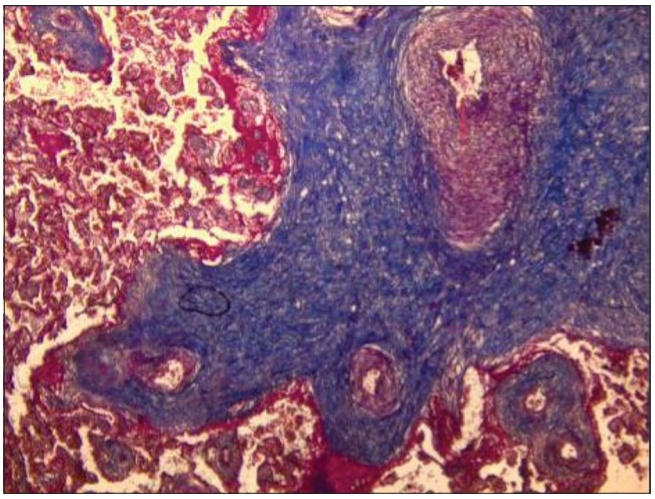

Figure 3: Medial hypertrophy in stem villi artery in preeclampsia. (Masson's Trichrome, ×10)

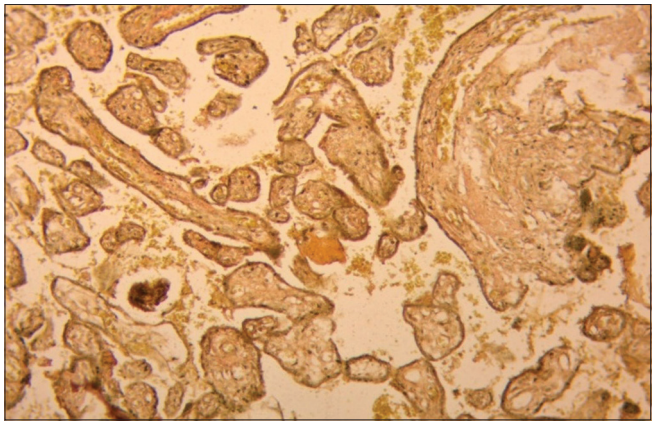

Figure 4: Normal elastic content in terminal villi capillaries in the control group (Verhoeff's stain, ×10)

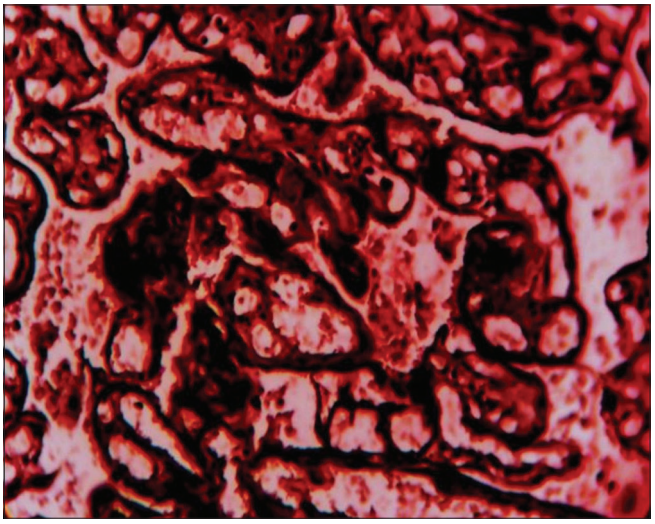

Figure 5: Increased content of elastic content in preeclampsia. (Verhoeff's stain, ×10)

to the mild preeclampsia and control group. These findings are similar to the study done by Stenmark *et al*.[8] Increased pressure in preeclampsia causes proliferation and elastin secretion of the smooth muscle cells leading to thickening of the vessel wall. This hypertrophy may be a protective mechanism adapted by the placental blood vessel tree against local stress. Similar findings were found by Las Heras and Haust[13,14] using electron microscopy, which showed increase in proliferation of smooth muscle cells in the media of stem villi arteries in toxemic placentae. Similar finding was observed by Baran *et al*. using Verhoeff's stain.[15]

In this study, the mean medial thickness in preeclampsia was 21.2 um in severe preeclampsia and 19.11 um in mild preeclamsia and 6.43 um in the control group. This measurement of media hypertrophy was not described in the literature, and exponential 30% increase of mean diameter bêtween preeclampsia and control group has been described.[16]

The findings of avascular villi and elastic content in terminal villi were significantly higher in cases of preeclampsia as compared to control ($P < 0.001$). Elastic stain was looked for in the blood vessel wall of terminal villi by using Verhoeff's stain. This elastic villus was increased in all cases of severe preeclampsia as compared to on severe preeclampsia and control group. This finding was compared with studies done by Baran *et al*.[15] using Verhoeff's stain and Stenmark *et al*.[8] which also showed a significant increase of elastic fiber in terminal villi, which was dark in color.

We already know that elastic tissue fibers increase in systemic hypertension; therefore, increase in elastic tissue fibers in placental terminal villi during preeclampsia may be induced by hypertension, which is a part of the protective mechanism.

Conclusion

Vascular changes in the villi of the preeclampsia placenta are the basis of the other gross and microscopic changes in the placenta. These changes may bring about differences in the function of the placenta.

Quantitative determination of placental changes is essential in the study of the placenta as normal pregnancies can also show similar placental changes due to aging. Vascular changes and products released may be the reasons for the onset of disseminated intravascular coagulation, maternal inflammatory syndrome, and poor fetal outcome in preeclampsia. More studies in this regard should be done**.**

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Nil.

Conflicts of interest

There are no conflicts of interest.

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